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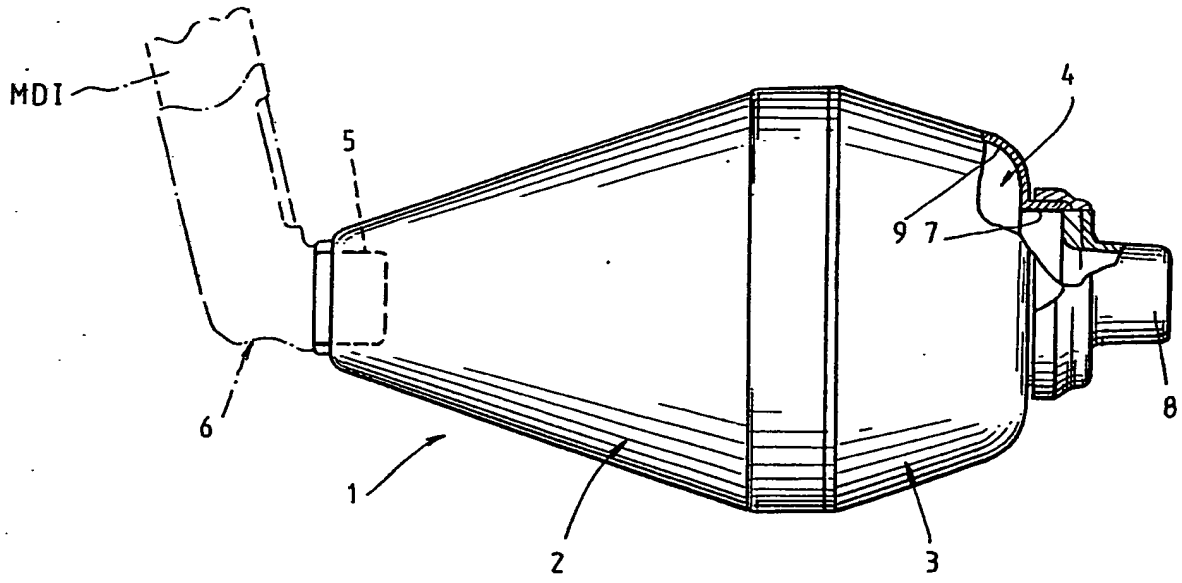
(54) Title: IMPROVEMENTS IN THE ADMINISTRATION OF AEROSOL COMPOUNDS



(57) Abstract

A device (1) for the administration of compounds in aerosol or suspended powder form comprising a cavity (4) into which the compound is to be introduced and a passage (7) through which the user inhales the compound from the cavity (4), the cavity having an exposed internal surface (9), said surface (9) being coated by means of an anti-static spray to reduce the tendency for particles of the compound to be attracted to said surface to thereby increase the delivery of the compound to the patient.

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TITLE: **IMPROVEMENTS IN THE ADMINISTRATION OF AEROSOL COMPOUNDS**

Field of the Invention

This invention relates to the improvements in the delivery of drugs and other compounds in aerosol form to patients via devices known as "spacers" or "aerosol holding chambers".

Background of the Invention

The delivery of anti-asthma medications by metered dose inhalers is plagued by problems of poor co-ordination. Devices known as spacers or aerosol holding chambers are now widely recommend to aid drug delivery from metered dose inhalers. They are claimed to increase the administration of the drug dose to patients, especially those with poor co-ordination. Spacer devices currently commercially available include The Nebuhaler, Volumatic, Aerochamber, Mizer, Inhal-aid, Inspirease, Nebuhaler, Fisonair and Babyhaler.

The Volumatic spacer has a volume of about 750ml and is moulded in two halves from polycarbonate. The Fisonair is also made from polycarbonate and has a silicone rubber valve. Some spacers may have face mask attachments and other spacers may have their chambers formed in the nature of a bellows which is collapsed to "pump" the drug to the patient.

Moulded plastic coffee cups may be adapted for use as spacers by cutting a hole in the bottom of the cup for insertion of the metered dose inhaler, with the mouth of the coffee cup being blocked with the hand or pressed directly over the face of the patient. Similarly, the drug may be discharged from an inhaler into the mouth of an inflatable chamber, such as a plastic bag, from which the drug is subsequently inspired through the mouth of the bag.

As a result of studies conducted on the output of various anti-asthma drugs from spacer devices, it has been concluded that the amount of drug contained in particles less than 5um in size, and thus likely to reach the lungs, that exits the spacer is relatively small. Research has led to the conclusion that the

small particles of drug contained in the aerosol delivered to the spacer device generate a static charge which causes the drug particles to be attracted to the sidewalls of the chamber, thereby resulting in such particles not reaching the lungs of the patient.

Summary of the Invention and Object

It is an object of the present invention to provide a modified spacer device and a method of delivering compounds in aerosol form to users in which the attraction of small particles within the aerosol to the walls of the spacer chamber is significantly reduced thereby increasing the amount of compound available in the chamber to reach the lungs of the patient.

Accordingly, the invention provides a device for the administration of compounds in aerosol or suspended powder form, such as a spacer, aerosol holding chamber or ventilator tubing, comprising a cavity into which the compound in aerosol or suspended powder form is to be introduced and an outlet through which the user inhales the compound from the cavity, each having an exposed internal surface characterised by means provided on said surface of at least the cavity for reducing the tendency for particles of the compound to be attracted to the exposed internal surface of the cavity to increase the delivery of the compound to the patient.

It is believed that a static charge is carried by the particles of compound introduced into the chamber and that these particles are attracted by the build-up of static charge on the internal surfaces of the cavity.

The suppression of the static electric properties of the internal surface of the cavity may be achieved in numerous ways, including :

(a) coating of the internal surface of the cavity by means of an anti-static spray, such as the commercially available product Statique manufactured by Allendale Products;

(b) the coating of the internal surface of the cavity with a sticky substance, such as honey or a greasy compound, such as petroleum jelly;

(c) moistening the internal surface of the cavity to decrease its static attraction;

(d) by physically roughening the internal surface of the cavity to reduce its ability to carry a static electric charge,

(e) lining the internal surface of the cavity or constructing the cavity from a material having conductive or otherwise anti-static properties, or

(f) prelining the internal surface of the cavity with a coating of the compound to be administered.

In some cases, the compound may be introduced into the patient's lungs by means of a ventilator via ventilation tubing. In such circumstances, the internal surfaces of the tubing and the face mask are treated or formed as defined above.

The cavity may be defined by an inflatable bag-like device formed from or lined with a conductive plastics material. In such a case, the drug is introduced into the mouth of the bag and is then inhaled from the bag through the mouth of the bag.

The invention also provides a method of delivering a compound in aerosol or suspended powder form to a user, comprising the steps of providing a spacer, an aerosol holding chamber or ventilator tubing including a cavity into which the compound is introduced in aerosol or suspended powder form and having a passage through which the user inhales the compound from the cavity, modifying the internal surface of at least the cavity to reduce the tendency of the compound to be attracted to the internal surface, and introducing the compound to be delivered to the user into the cavity and delivering the compound to the user by inhalation from the cavity.

The anti-static properties of the internal surface of the cavity may be modified in any one of the manners described in greater detail above.

Brief Description of the Drawings

One embodiment of the invention will now be further described with reference to the accompanying drawings in which the inventi n will now be described further with reference to the accompanying drawings in which :

Figure 1 is a side elevation, partly in section, of a typical spacer device modified in accordance with the invention;

Figures 2 and 3 are graphs illustrating experimental data applicable to the delivery of Salbutamol from a metered dose inhaler via a Volumatic spacer, and

Figures 4 and 5 are similar graphs illustrating experimental data relating to the delivery of Sodium cromoglycate from a 5mg metered does inhaler via a Fisonair spacer.

Description of Preferred Embodiment

Referring firstly to Figure 1 of the Drawings, the spacer illustrated in this Figure is a Fisonair spacer, which is typical of the commercially available spacers or aerosol holding chambers. The spacer comprises a two part chamber (1) comprising an aerosol section (2) and a mouthpiece section (3), which are joined together to define a hollow internal cavity (4). The aerosol section has an inlet opening (5) which receives a shaped holder (6) which is adapted to receive a metered dose inhaler (MDI) of known construction. The mouthpiece section (3) has an outlet opening (7) to which a removable mouthpiece (8) is attached. In accordance with the invention, the internal surface (9) of the cavity defined by the aerosol and mouthpiece sections (2) and (3), as well as the outlet passage (7) is coated with anti-static spray, such as Statique, and allowed to dry for twenty four hours.

As mentioned above the internal surface (9) may be modified to reduce the tendency for particles of the drug to be attracted to the surface in other ways, as described in greater detail above, and the invention is not limited to the application of anti-static sprays or the like to the internal surface (9). Of course, in any commercial application of the invention, the internal surface (9) would be most conveniently metallised or coated with a more permanent anti-static coating, such as a coating or film of plastics material having anti-static properties, for example non-toxic conductive polyethylene or polypropylene. Alternatively, the spacer, as well as any valves and mouth pieces, may be formed from such plastics.

The experimental evidence presented in Figures 2 to 5

clearly illustrate that the drug available to patients, in respirable particles (less than 5 um), has been markedly increased by a simple structural modification to existing Volumatic (Glaxo) and Fisoair (Fisons) spacer devices.

Salbutamol and sodium cromoglycate were actuated from metered dose inhalers (MDI) into spacer devices and drawn into a multistage liquid impinger which divides aerosol into various particle size fractions. Drug contained in these fractions was assayed by HPCL (Salbutamol) and by a spectrophotometric method (Sodium cromoglycate).

Referring to Figure 2, only 12.2(SD=2)ug of Salbutamol (per 100 ug actuation into the Volumatic device) contained in particles <5 microns was available for immediate inhalation. As shown in Figure 3, this decreased to 1.7(SD=0.4)ug if the drug was retained in the spacer for 20 seconds prior to inhalation.

Following spacer and actuator modification by coating the internal surface of the spacer with Antistatic spray and allowing to dry for 24 hours, salbutamol available for immediate inhalation increased to 45 (SD=4)ug and to 39(SD=4)ug if retained for 20 seconds prior to removal. Improvement is also evident where honey is the coating material.

This represents a 368% and 2294% increase in salbutamol available for inspiration immediately after and at 20 seconds following actuation.

Referring to Figure 4, only 0.26(SD=0.04)mg of sodium cromoglycate (5mg/actuation into the Fisonair spacer) in particles <5um was available for immediate inspiration, and 0.12(SD=0.03)mg at 20 seconds (Figure 5). Following spacer and actuator modification by coating the internal surface of the spacer with Antistatic spray and allowing to dry for 24 hours, this increased to 0.79(SD=0.02)mg available immediately and 0.56 (SD=0.03) ug at 20 seconds; an increase of 303% and 466% respectively. The improvement achieved by the use of honey is also evident in Figure 4.

The MMAD(SD) and GSD(SD) for aerosol leaving the spacer devices was 2.8(0.2) and 1.6(0.1) for salbutamol and 3.8(0.2) and 1.7(0.2) for sodium cromoglycate.

The data presented in Figures 4 and 5 clearly indicate that the effective delivery of sodium cromoglycate is substantially improved by coating the internal surface of the Fisonair spacer with an anti-static spray, in the present case, the commercially available product Statique. Significant improvement in delivery is achieved by coating the internal surface of the Fisonair spacer with honey, and it is expected that improvements will result from other methods of increasing the anti-static properties of the internal surface of the spacer, such as by coating with grease or petroleum jelly, by physically roughening the internal surface of the spacer, or by forming a conductive coating for example a suitable thin metal film or coating, on the internal surface of the spacer to reduce its ability to carry a static charge.

As mentioned above, the internal surface of the spacer may be lined with a coating of a suitable anti-static material, such as non-toxic conductive polyethylene or polypropylene, or the spacer may be moulded from a plastics material having anti-static properties. Similarly, the surface may be coated with the drug being used to suppress the attractive charge on the surface.

Recently conducted tests on a Fisonair spacer with a non-toxic conductive polyethylene film lining its internal surface have exhibited an improvement in delivery of sodium cromoglycate to the patient from 0.725mg without the lining to 1.69mg with the lining (from 0.28mg to 0.47mg in particles less than < 5 um).

It will be appreciated that the invention provides a dramatic increase in the availability of drug for inhalation from a treated spacer or aerosol holding chamber and the implications with regards to increased therapeutic effect and reduced treatment cost using this method are quite considerable.

Claims :

1. A device for the administration of compounds in aerosol or suspended powder form, such as a spacer, aerosol holding chamber or ventilator tubing, comprising a cavity into which the compound in aerosol or suspended powder form is to be introduced and an outlet through which the user inhales the compound from the cavity, each having an exposed internal surface, characterised by means provided on said surface of at least the cavity for reducing the tendency for particles of the compound to be attracted to the exposed internal surface of the cavity to increase the delivery of the compound to the user.

2. The device of claim 1, wherein said surface of at least the cavity is at least coated with a material selected from an anti-static compound, a sticky or greasy compound, a compound of the type to be administered or a conductive material.

3. The device of claim 1, wherein said surface of at least the cavity is physically roughened to reduce its ability to carry a static electric charge.

4. The device of claim 1, wherein said surface is covered by at least a film of non-toxic conductive plastics material.

5. The device of claim 1 wherein said cavity is formed in a body of non-toxic conductive plastics.

6. A method of delivering a compound in aerosol or suspended powder form to a user, comprising the steps of providing a spacer, an aerosol holding chamber or ventilator tubing including a cavity into which the compound is introduced in aerosol or suspended powder form and having an outlet through which the user inhales the compound from the cavity, modifying the internal surface of at least the cavity to reduce the tendency of the compound to be attracted to the internal surface, and introducing the compound to be delivered to the user into the cavity and delivering the compound to the user by inhalation from the cavity.

7. The method of claim 6 comprising forming a coating on the internal surface of at least the cavity of a material selected from an anti-static compound, a sticky or greasy compound, a compound of the type to be administered or a conductive material.

8. The method of claim 6, comprising the step of physically roughening the internal surface of at least the cavity to reduce it ability to carry a static electric charge.

9. The method of claim 6, wherein said internal surface is covered by at least a film of non-toxic conductive plastics material.

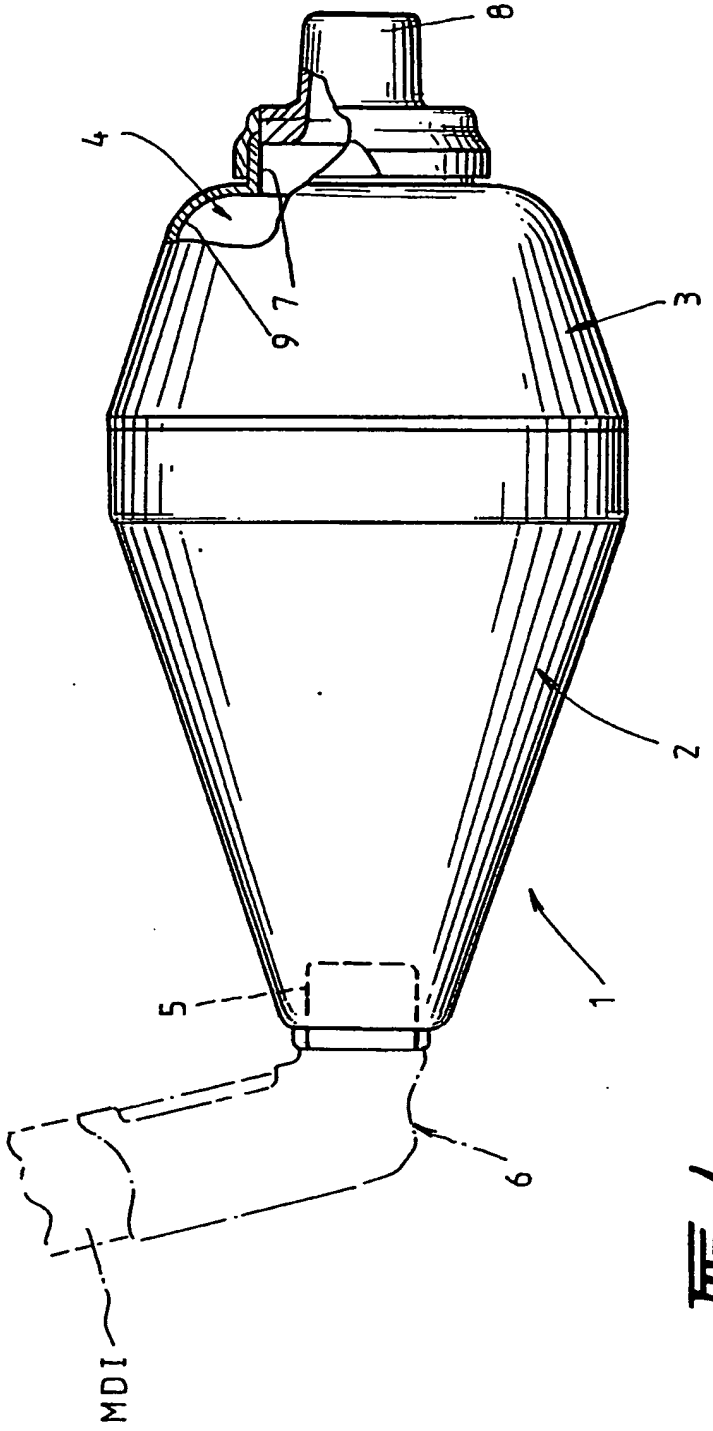


FIG. 1.

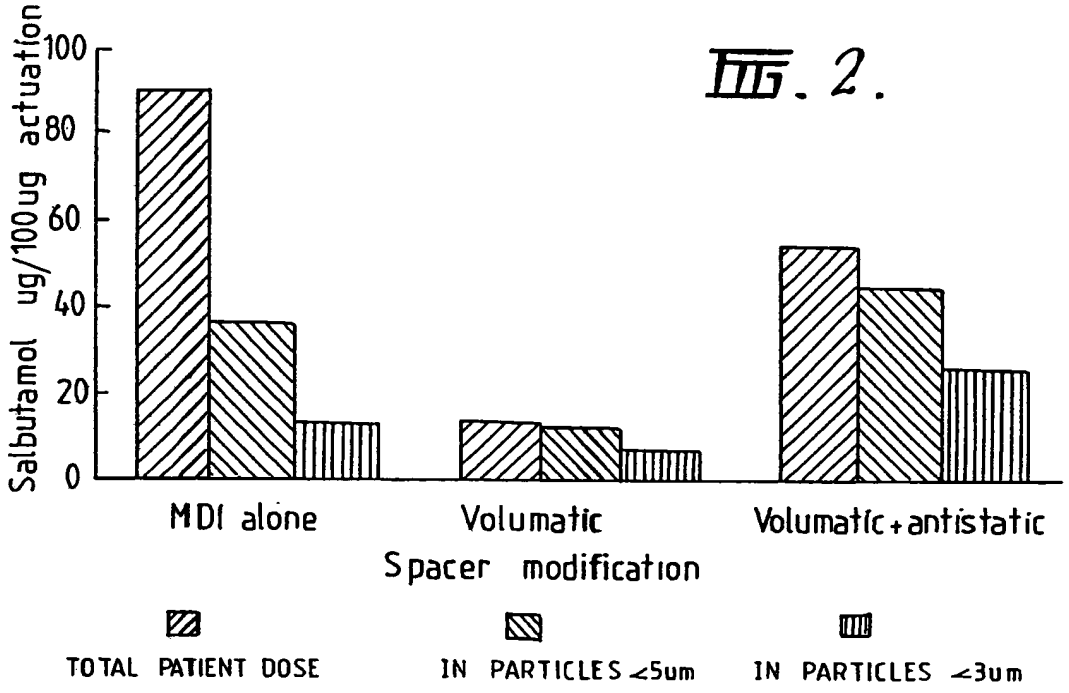
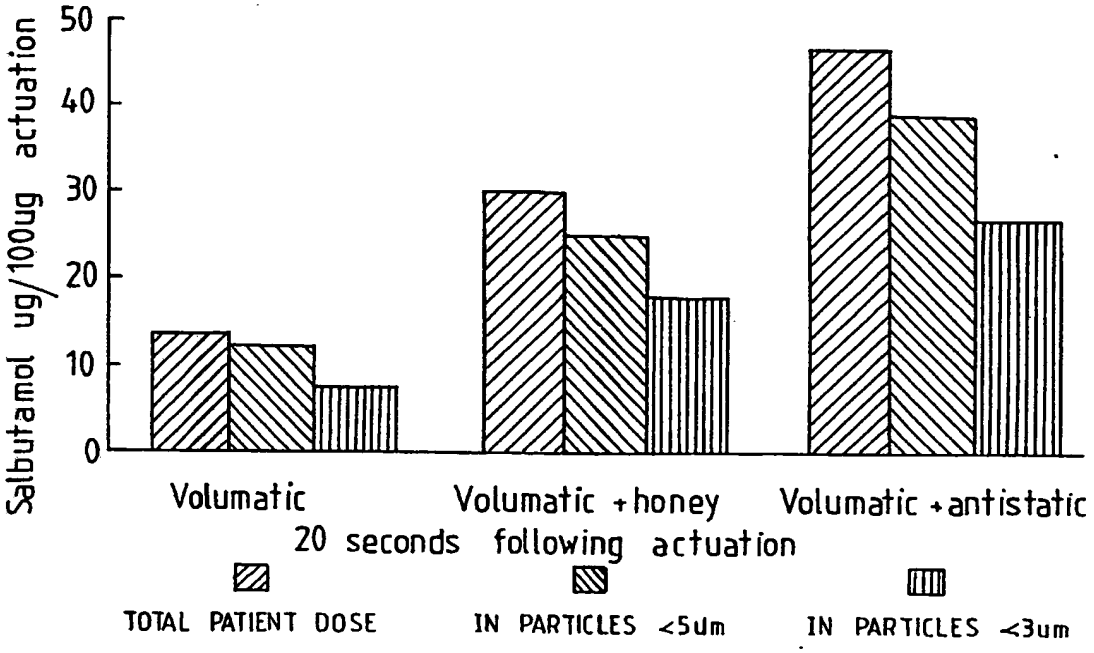


FIG. 2.



Volumatic surface and residence time

FIG. 3.

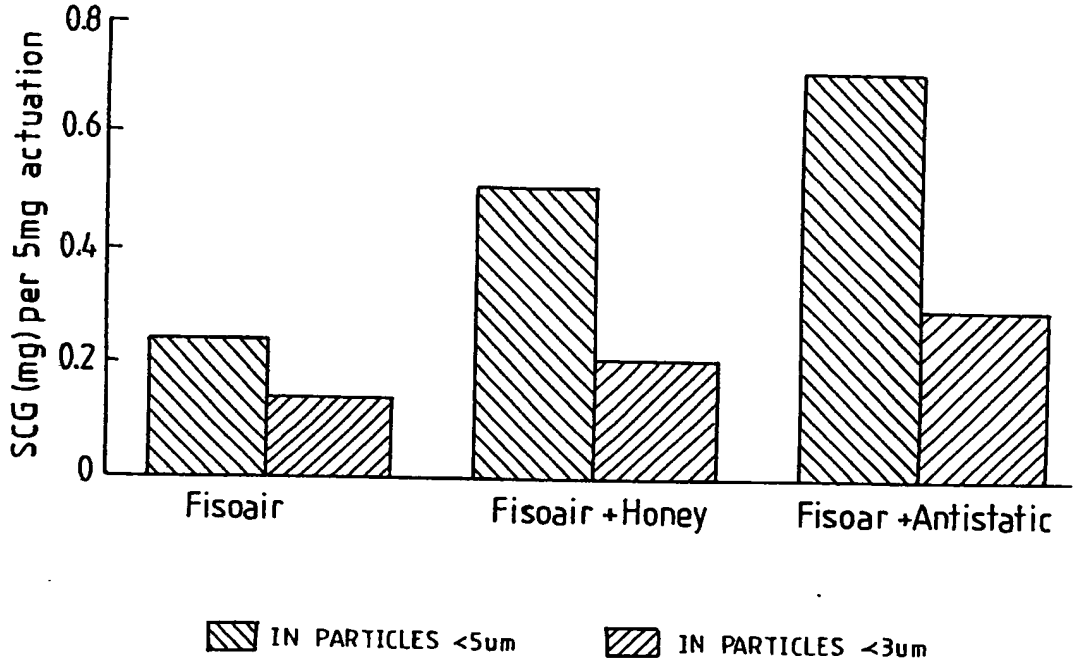

SCG (mg) per 5mg actuation
0.8
0.6
0.4
0.2
0
Fisoair
Fisoair +Honey
Fisoar +Antistatic
IN PARTICLES <5um
IN PARTICLES <3um

FIG. 4.

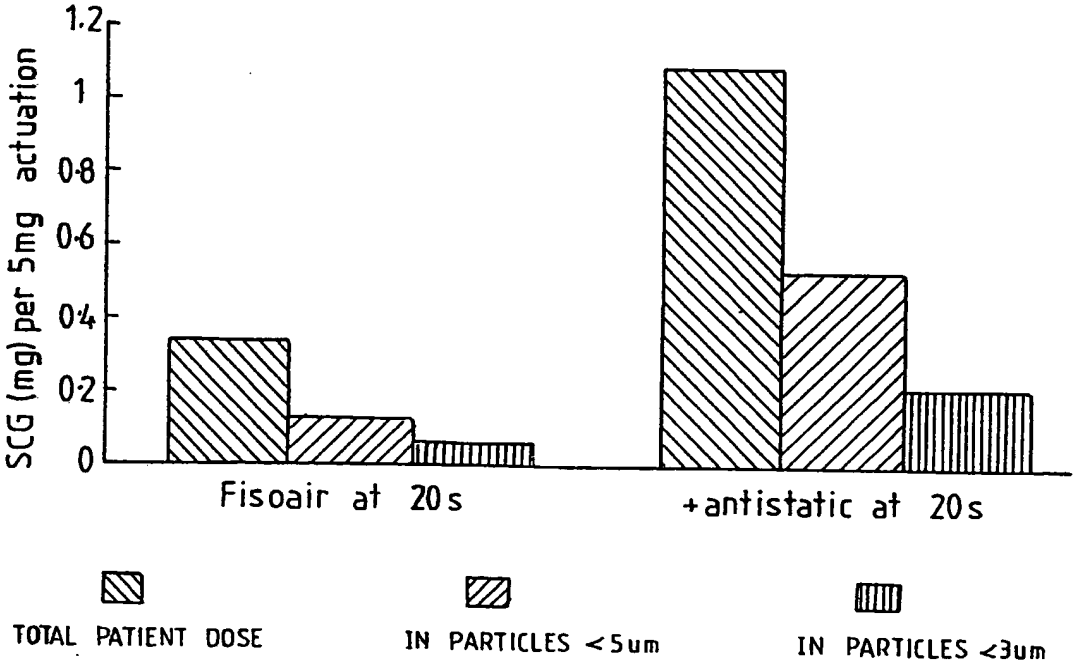

SCG (mg) per 5mg actuation
1.2
1
0·8
0·6
0·4
0·2
0
Fisoair at 20s
+antistatic at 20s
TOTAL PATIENT DOSE
IN PARTICLES <5um
IN PARTICLES <3um

FIG. 5.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU92/00668

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.[5] A61M 13/00, 15/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC A61M 13/00, 15/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
AU: IPC as above

Electronic data base consulted during the international search (name of data base, and where practicable, search terms used)
DERWENT: (a61M 13/- or 11/- or 15/-) and (static or antistatic or electrostatic)
JAPIO

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	GB,A, 1459426 (ALLEN & HANBURYS LTD) 22 December 1976 (22.12.76). See page 2 lines 54-57	1-9
P,X	WO,A, 91/19524 (RHONE-POULENC RORER LTD) 26 December 1991 (26.12.91). See page 8 line 25-page 9 line 33	1-9
X	US,A, 4240418 (ROSSKAMP et al) 23 December 1980 (23.12.80). See column 7 lines 14-17	1-9

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
15 February 1993 (15.02.93)	22 FEBRUARY 1993 (22.02.93)

Name and mailing address of the ISA/AU	Authorized officer
AUSTRALIAN PATENT OFFICE PO BOX 200 WODEN ACT 2606 AUSTRALIA	JOHN HO
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This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
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		CH	563168	DE	2408791	FR	2218905
		IT	1008929	JP	50025092	NL	7402230
		US	3858583	ZA	7400553		
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		AT	2856/83	DE	2524902	SE	7509343
		DE	2529522				
WO	8303976	US	4484577	EP	108145	EP	50654
		JP	2131747				

END OF ANNEX